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BLOOD LIPID RESPONSES TO DECOMPRESSION SICKNESS

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13. ABSTRACT

Initial studies were conducted to determine the role of circulating lipids in the etiology of decompression sickness and to evaluate liver and adipose tissues as possible sources of embolic lipid. It was found in in vitro studies with rat liver slices that pressurization alone may be an inadequate stimulus for initiation of excessive liver lipid biosynthesis, and that an inadequate decompression may not result in a significant lipid loss from liver (and also adipose) tissue.

Experiments were performed employing various agents known to affect various aspects of lipid metabolism. These agents were administered to rats which were subsequently exposed to a pressurization profile that i untreated animals resulted in noticeable decompression sickness, but did not normally result in fatality. Effectiveness of the treatment wa determined by comparison with an untreated control population. The implications from this study were:

(1) the levels of circulating lipids (triglycerides) have little if any effect on decompression sickness.

(2) Circulating free fatty acids have a profound effect on decompressio sickness--symptoms are increased with low fatty acid levels and decreased with highr levels.

(3) Ionic calcium concentrations are possibly involved in the etiology of decompression sickness.

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Circulating lipids are reportedly involved in the obscure etiology of decompression sickness (1). Certain studies carried out after the occurrence of severe decompression sickness reported the presence of lipid emboli in the lungs of the affected animals (2,3). Heparin administration ameliorated the occurrence of decompression sickness (4,5) and concurrently decreased serum turbidity (6).

Prior observations that heparin reduced the concentration of circulating lipids was employed by Philp et al (6) to propose a potentially detrimental role for circulating lipids in decompression sickness. Additional substantiating evidence has not been obtained. The origin of enhanced levels of circulating lipid for involvement in decompression sickness has remained as obscure as their definitive role in this process. Rait (7) has attempted to implicate a role for a fatty liver in decompression sickness without substantive documentation. Body fat could be a source for embolic lipids but insufficient data are available to document this possibility (8). The occasional appearance of bone marrow emboli in the lungs of animals that incurred decompression sickness (9) could be interpreted to imply that bone marrow is a potential source for embolic lipid. These studies were undertaken to gain insight into the role of circulating lipids in the etiology of decompression sickness and to evaluate liver and adipose tissues as possible sources for embolic lipid. Additional insight into these questions should assist in understanding the etiology of decompression sickness.

Preliminary <u>in vitro</u> studies were carried out to determine the response of liver and adipose tissue to pressurizations with subsequent

inadequate decompressions. In vitro liver slices were subjected to pressurized environment at both normal and increased oxygen tensions. The incorporation of carbon-14 labeled acetate into liver lipid during the pressurization was employed to ascertain the effect of the pressurized environment on liver lipid metabolism. At normal oxygen tensions, the pressurized environment did not affect the uptake of radiolabel into liver slices, nor did the inadequate decompressions alter the amount of radiolabel present in the liver slice (10). An increase in oxygen tension increased the incorporation of radiolabel into liver lipid, but was pressure independent (10).

Adipose tissue sections containing carbon-14 labeled lipid were subjected to a presssurized environment followed by a severely acute decompression schedule. The decompression profile was sufficiently inadequate to induce numerous gas bubbles in the adipose tissue sections. Even in the presence of potentially disruptive gas bubbles, no reduction in the level of carbon-14 labeled lipid was observed in the adipose tissue sections after the pressurization. Epinephrine-stimulated lipolysis was studied under these same conditions. No significant differences were observed between the control and the pressurized adipose tissue sections. Lipid release from adipose tissue resultant from either a mechanical tissue disruption by gas bubbles or an enhanced hormone-stimulated lipolysis was not observed in the completed studies. These observations would suggest that pressurization alone may be an inadequate stimulus for initiation of excessive liver lipid biosynthesis, and that an inadequate decompression may not result in a significant lipid loss from either liver or adipose tissue.

To further elucidate a possible role for lipid in the etiology of decompression sickness, various agents were exogeneously administered

to male Sprague Dawly rats. The rat was subsequently exposed to a pressurization profile that resulted in noticeable decompression sickness, but was not sufficiently sever to induce a high number of fatalities. Each animal was employed one time. Most of the agents utilized either enhanced or decreased circulating lipids by one manner or another on a time course sufficiently adequate to have maximal activity during and immediately after the inadequate decompression. The observed symptoms of decompression sickness in the treated population, Table I, were compared to an untreated control population to determine the effectiveness of the treatment. Table II describes the observations and statistical analysis of these comparisons.

A carbon tetrachloride altered liver (11) did not significantly modify the observed symptoms of decompression sickness. This observation suggests that liver lipid might not detrimentally interact with the occurrence of decompression sickness as was suggested by the in vitro studies. The exogenous administration of lipid (corn oil fed animals) with a concurrent significant enhancement of the circulating chylmicron levels did not affect the occurrence of decompression sickness. A rapid transfer of lipid between the chylymicron and low-density lipoproteins has been documented. (12). These data would suggest that the presence of excessive levels of circulating lipoproteins did not affect the eventual occurrence of decompression sickness in the treated animals. Thus, the presence of excessive circulating lipids was not detrimental to the animal as has been observed in altitude decompression sickness (13). The symptoms of decompression sickness have been related to the symptoms of disseminated intravascular coagulation (14), a condition that can be induced by the presence of embolic levels of circulating free fatty acids (15).

Methylprednisolone succinate (SOLU-MEDROL) has been employed to ameliorate the effects of peripheral shock (16) and the effects of exogenously administered embolic free fatty acids (17). The administration of methyl predisolone succinate in these studies did not significantly alter the observed symptoms of decompression sickness suggesting that embolic levels of free fatty acids were not contributing to the eventual occurrence of decompression sickness. Heparin significantly ameliorated the occurrence of decompression sickness as has been previously reported (4,5,6). Nicotinic acid lowers the level of circulating triglycerides and free fatty acids in the fasted animal (18). The administration of nicotinic acid in these studies resulted in a very significant enhancement of fatal decompression sickness. A review of the above results suggests that the presence of excessive lipid is not harmful with respect to decompression sickness, while the lowering of specific circulating lipid levels may occur to the detriment of the treated animal.

Heparin lowers the level of circulating lipids through the activation of lipoprotein lipase (19). Lipoprotein lipase enzymatically hydrolyzes the lipids in low molecular weight lipoproteins to glycerol and free fatty acids (20). Thus, concurrent with the reduction in complex lipids affected by heparin, a rise in circulating free fatty acid levels must occur. The increased level of circulating free fatty acids does produce embolic levels of fatty acids since heparin does not result in the occurrence of disseminated intravascular coagulation. When circulating free fatty acid levels were intentionally lowered in these studies (nicotinic acid), an enhancement of fatal decompression sickness was observed. Thus, the presence of increased levels of circulating free fatty acids resultant from the administration of

heparin could be an ameliorating factor in the subsequent occurrence of decompression sickness. The rapid turnover rate of free fatty acids (21) precludes an effective analysis of their circulating levels. Therefore, indirect approaches must be used to elucidate or verify an ameliorative role for transient increases in circulating free fatty acids in decompression sickness.

Heparin administration reportedly lowers the level of circulating ionic calcium through the formation of calcium-fatty acid salts (22). The occasional observance of bone marrow emboli in severely decompressed animals indicates that bone alterations could occur pursuant to decompression sickness. The observation of significant reductions in bone density (23) in inadequately decompressed animals, Table II, verified the removal of calcium from bone either during or pursuant to the occurrence of decompression sickness. If the ameliolative role of elevated free fatty acids in decompression sickness is due to lower circulating ionic calcium levels, then the exogenous administration of calcitonin should have a similar effect. The administration of porcine calcitonin in these studies very significantly reduced the occurrence of decompression sickness. Thus, it appears possible an interaction between the heparin-stimulated elevations in circulating free fatty acids and inadequate decompression-stimulated elevations in circulating ionic calcium levels could occur to the benefit of the inadequately decompressed animal.

Marked hemoconcentration is known to occur in decompression sickness (24). The distribution and location of the fluids lost from the vascular system is not known, nor has the time course for a return to normal fluid dynamics been established. Total serum calcium

concentrations in the rat one hour after the pressurization were normal in these studies, except in the calcitonin treated animals. Total serum calcium measurements reflect the sum of the ionic calcium levels and bound calcium levels. Thus, a sequestration of calcium at some site and/or a shift within the distribution of calcium types in the total calcium measurement must occur to explain the observation that total serum calcium levels seemed invariant. Ionic calcium is considered a primary biological messenger (25) and significant level variations should result in widely divergent behavioral observations. Many of the anticipated behavioral observations (26,27,28) are consistent with observations in decompression sickness; however, total agreement is not evident. Marked elevations of urinary calcium levels have been observed in man up to 48 hours after the occurrence of decompression sickness (29). The physiological similarities between various acute hypercalcemias and the delayed excretion of calcium after decompression sickness suggests a role for calcium in the etiology of decompression sickness. The lowering of calcium levels by the action of calcitonin or by interaction with circulating free fatty acids, with a concurrent reduction in the symptoms of decompression sickness, suggests a detrimental role for calcium in decompression sickness and a beneficial role for elevated circulating fatty acids.

The results and observations of these studies do not conclusively document the role of lipids in the etiology decompression sickness. However, sufficient data were collected and sufficient observations derived to demonstrate an ameliorative role for lipids in decompression sickness, and to suggest a possible pathway for this action.

TABLE I. SUBJECTIVE SYMPTOMS OF DECOMPRESSION SICKNESS [a]

DECOMPRESSION SICKNESS SYMPTOM	ABBREVIATION
Light Respiratory rate changes	Lr
Heavy Respiratory changes, gasping, etc.	Hr
Discoordinate movement, vertigo, etc.	Disc
Minor paralysis, hind leg(s)	Min
Major paralysis, hind leg(s)	Maj
Paralysis, foreleg and hind leg	Para
Death	Death
No symptoms	Ns

[a] Animals observed for a maximum of one hour post dive on slow moving flat bed treatmills. For a further description of each symptom see (23).

TABLE II - EFFECT OF VARIOUS TREATMENT REGIMENS ON THE SYMPTOMS OF DECOMPRESSION SICKNESS.[a]

TREATMENT	N[c]	SYMPTOM PER CENT DISTRIBUTION[b] Lr	Hr	Disc	Min	Maj	Para	Death	Ns
Control Dive, No Treatment	46	15.2	71.7	21.7	13.0	60.9	17.4	10.9	4.3
Carbon Tetrachloride in oil[d]	10	30.0	70.0	30.0	30.0	30.0	10.0	10.0	---
Corn Oil fed[e]	8	12.5	75.0	37.5	---	37.5	---	12.5	12.5
Methylprednisolone succinate[f]	12	33.3	66.7	25.0	41.7	25.0	8.3	33.3	---
Heparin[g]	8	50.0*	25.0*	25.0	37.5	25.0	---	---	25.0
24 hr. Fast[h]	8	37.5	62.5	12.5	12.5	37.5	12.5	37.5	---
24 hr. Fast + Nicotinic Acid[i]	8	12.5	37.5	12.5	---	50.0	37.5	62.5**	---
Calcitonin[j]	12	16.7	41.7	16.7	16.7	25.0	---	8.3	41.7

[a] Statistics derived employing enumeration techniques (23);

[b] per cent of number of animals in treatment group, one or more symptoms may occur in each animal;

[c] Number of animals in each treatment group;

[d] 0.46 mg/kg CCl4 administered i.p. in mineral oil pre-dive, sham mineral oil treatment of dived animals did not produce significant variances;

[e] Animals fasted with water 48-24 hr pre-dive, fed corn oil soaked chow for 24 hours preceding dive, serum chylimicron levels significantly increased post dive;

[f] 32 mg/kg administered i.m. pre-dive as SOLU-MEDROL:

[g] 8000 units/kg administered pre-dive;

[h] chow withheld, water ad.libidum;

[i] 250 mg/kg administered in saline as the potassium salt pre-dive;

[j] 220 units/kg porcine calcitonin administered s.c. in gelatin pre-dive.

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